

## REMARKS

Upon entry of the present Amendment, claims 1 and 3-23 will be pending. Claim 2 is canceled. Applicant reserves the rights to pursue the withdrawn and/or canceled subject matter in a subsequent application. Support for amended claim 1 for reciting “said carrier macromolecule is water soluble at a temperature in the range of 0-60°C” can be found throughout the application and, *inter alia*, at page 11, lines 26-35 and page 12, lines 26-32 of the present specification. Support for amended claim 3 for reciting “said carrier macromolecule is a natural gum or a homopolyamino acid” can be found throughout the application and, *inter alia*, in original claims 1 and 2. Support for amended claim 21 for reciting “which non-nucleotide carrier macromolecule is directly bound to a solid support” can be found throughout the application and, *inter alia*, at page 7, lines 1-4 of the present specification. Support for new claim 23 can be found throughout the application and, *inter alia*, in original claims 1 and 7. Various claims are also amended for formality reasons. The above-described amendments do not introduce any new matter into the present application.

### Claim Objections

Claims 1 and 3 are objected to because of the following informality: “extending said primer to form an extended primer which replicates said template in complementary form” should be “extending said primer to form an extended primer which replicates from said template”.

This objection is overcome by the amendments of claims 1 and 3 as suggested by the Examiner.

Claim 8 is objected to because of the following informality: “the action of polymerase incorporating nucleotides on to said primer” should be “the action of a polymerase wherein the polymerase incorporates nucleotides into said primer”.

This objection is overcome by the amendment of claim 8 as suggested by the Examiner.

Claim 7 is objected to because of the following informality: "on of the two vinyl groups" should be "one of the two vinyl groups" in order to correspond to claim 7 filed on February 13, 2003.

This objection is overcome by the amendment of claim 7 as suggested by the Examiner.

Claim 9 is objected to because of the following informality: "(3sr" should be "(ssr)".

This objection is overcome by the amendment of claim 9 as suggested by the Examiner.

Claim 10 is objected to because of the following informalities: (1) "single; stranded form" should be "a single stranded form"; and (2) "a first one of the template stranded" should be "one of the template strand".

Although the Examiner indicates that the above objection is directed to claim 10, it seems that it should have been directed to claim 11. This objection is overcome by the amendment of claim 11 as suggested by the Examiner.

Claim 22 is objected to because of the following informality: "utilizing a primer or a hybridization probe" should be "utilizing said primer or said hybridization probe".

This objection is overcome by the amendment of claim 22 as suggested by the Examiner.

Claim 20 is objected to because of the following informality: in order to better define said extend primer, examiner suggests that applicant changes the phrase "said extended primer having a sequence complementary to said sequence to be detected bound to said carrier macromolecule" to "said extended primer that has a sequence complementary to said sequence to be detected and is bound to said carrier macromolecule"

This objection is overcome by the amendment of claim 20 as suggested by the Examiner.

### **Rejections under 35 U.S.C. § 112**

Claims 7-17 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 7 is rejected as allegedly vague and indefinite in view of the phrase “each of which moieties is attached to each of the carrier macromolecule and the primer by a covalent linkage; formed between one of the two vinyl groups of a divinyl sulphone molecule and a reactive functionality on the carrier macromolecule or primer.” The Examiner states that according to the first part of the phrase, it appears that both carrier macromolecule and primer contain one or more moieties from divinyl sulphone. The Examiner also states that, however, the second part of the phrase indicates that one of carrier macromolecule and primer contains one or more moieties from divinyl sulphone. The Examiner further states that the first part and the second part of the phrase do not correspond each other. The Examiner requests the Applicant to clarify the limitation at issue.

It is respectfully submitted that this rejection is overcome by the amendment of claim 7.

Claim 8 recites the limitation “the action of polymerase incorporating nucleotides on to said primer” in the claim. The Examiner states that there is insufficient antecedent basis for this limitation in the claim since there is no polymerase in claims 3-7. The Examiner requests the Applicant to clarify the limitation at issue.

It is respectfully submitted that this rejection is overcome by the amendment of claim 8.

Claim 13 recites the limitation “a second primer” in the claim. The Examiner states that there is insufficient antecedent basis for this limitation in the claim since there is no second primer in claims 1-8. The Examiner requests the Applicant to clarify the limitation at issue.

It is respectfully submitted that this rejection is overcome by the amendment of claim 13.

Claim 14 is rejected as allegedly vague and indefinite because it is unclear whether another primer recited in claim 14 and at least another primer recited in claim 10 are identical or not. The Examiner states that if another primer recited in claim 14 and at least another primer recited in claim 10 are identical, “another primer” in claim 14 should be “the another primer.” The Examiner requests the Applicant to clarify the limitation at issue.

It is respectfully submitted that this rejection is overcome by the amendment of claim 14.

Claim 15 is rejected as allegedly vague and indefinite because it is unclear whether said primer recited in claim 15 is another primer recited in claim 14 or at least another primer recited in claim 10 or the primer recited in claim 1. The Examiner requests the Applicant to clarify the limitation at issue.

It is respectfully submitted that this rejection is overcome by the amendment of claim 15, which clarifies that a detectable marker is incorporated into one of the extended primers.

Claim 16 is rejected as allegedly vague and indefinite because it is unclear whether the primer recited in claim 16 is the primer recited in claim 15 or another primer recited in claim 14 or at least another primer recited in claim 10 or the primer recited in claim 1. The Examiner requests the Applicant to clarify the limitation at issue.

It is respectfully submitted that this rejection is overcome by the amendment of claim 15, which clarifies that extension of one of the primers is conducted *in situ*.

It is respectfully submitted that the rejection of claims 7-17 under 35 U.S.C. § 112, second paragraph, is overcome by the above remarks and/or amendments and must be withdrawn.

### **Rejections under 35 U.S.C. § 102**

#### Claim 18

Claim 18 is rejected under 35 U.S.C. 102(b) as being allegedly anticipated by Houtz (US Patent No. 5,908,972, filed on July 29, 1996). The disclosure of Houtz is discussed in the previous Office Action and response. The Examiner states that the rejection is maintained because the content of claim 18 does not require a non-nucleotide carrier macromolecule.

It is respectfully submitted that this rejection is overcome by the amendment of claim 18, which now recites “a non-nucleotide carrier macromolecule.”

#### Claim 21

Claim 21 is rejected under 35 U.S.C. 102(b) as being allegedly anticipated by McCormick et al., (Promega Notes Magazine Number 40, 1993, p.04). Regarding claim 21, McCormick is alleged to teach to hybridize an oligonucleotide labeled with alkaline phosphatase with nucleic acids immobilized on a membrane (see Figure 2). The Examiner states that since alkaline phosphatase is directly and covalently attached to the oligonucleotide (see first page) and it is known that alkaline phosphatase has a molecular weight in excess of 80,000 Daltons, after the hybridization, alkaline phosphatase (i.e., a non-nucleotide carrier macromolecule) is indirectly bound to the membrane (i.e., a solid support) by the oligonucleotide.

It is respectfully submitted that this rejection is overcome by the amendment of claim 21, which now recites “the non-nucleotide carrier macromolecule is directly bound to a solid support.”

Claims 1 and 3-6

Claims 1 and 3-6 are rejected under 35 U.S.C. 102(e) as being allegedly anticipated by Dale et al., (US Patent No. 5,856,092, filed on April 1995).

According to the Examiner:

Regarding claims 1, 3, and 5, Dale *et al.*, teach a method for detecting whether a specific nucleotide or base is at a particular position in a specific polynucleotide sequence. The method comprises: a) exposing, under hybridizing conditions, said specific polynucleotide sequence to an oligonucleotide primer wherein said primer has a sequence complementary to part of the specific polynucleotide sequence wherein said primer has incorporated at its 5' end an element selected from the group consisting of a separation element and a detectable element, and wherein said primer hybridizes at a location selected from the group consisting of (i) immediately adjacent to the particular position and (ii) not immediately adjacent to the particular position whereby there is an intervening sequence between the particular position and primer bound to the specific polynucleotide sequence; b) extending said hybridized primer up to and including said specific nucleotide or base wherein the 3' terminal nucleotide is a ddNTP and further includes an element selected from the group consisting of a separation element and a detectable element with the proviso that said extended primer has at least one separation element and at least one detectable element; c) separating the product of step b) into fractions wherein one said fraction contains the primer extension product that contains the chain terminating nucleotide at said particular position; and d) determining whether said primer extension product having said chain terminating nucleotide at said particular position is present in said fraction by assaying said fraction wherein the assay does not include a digestion step wherein said separating step comprises contacting any extended primer with a molecule having affinity for the separation element, said molecule being linked to a support (i.e., cellulose or agarose) that facilitates said separating; and separating said contacted extended primer to provide said fraction (see lines 50-53 in column 16, claims 1 and 2 in column 39 and Figure 1). Since Dale *et al.*, teach a primer bound to a cellulose and it is known that cellulose is a complex carbohydrate, or polysaccharide consisting of 3,000 or more glucose units and glucose has a

formula of  $(C_6H_{12}O_6)$  with a molecular weight of 180.2 Daltons (see an attachment for cellulose), a cellulose has a molecular weight of 540,600 Daltons or more as recited in claim 5. Therefore, Dale *et al.*, disclose providing said primer being bonded to a carrier macromolecule having a molecular weight in excess of 80,000 Daltons (i.e., a cellulose) wherein said carrier macromolecule is a natural or synthetic polysaccharide or a cellulose derivative as recited in claims 1 and 3. Since Dale *et al.*, teach exposing, under hybridizing conditions, said specific polynucleotide sequence to an oligonucleotide primer wherein said primer has a sequence complementary to part of the specific polynucleotide sequence and extending said hybridized primer up to and including said specific nucleotide or base (see claim 1 in column 39, Dale *et al.*, disclose hybridizing the bound primer to said template and extending said primer to form an extended primer which replicates from said template as recited in claims 1 and 3.

Also according to the Examiner:

Regarding claims 4 and 6, since Dale *et al.*, teach that the support bound to the primer can be agarose (see lines 50-53 in column 16) and it is known that agarose is a natural polysaccharide with a molecular weight of about 120, 000 and can be dissolved in boiled water (see an attachment for agar), agarose taught by Dale *et al.*, is a carrier macromolecular as recited in claim 6. Since it is known that agarose is a linear polymer and can be used in gel electrophoresis at least at pH from 7 to 8 without altering its properties, claim 4 is anticipated by Dale *et al.*.

It is respectfully submitted that this rejection is overcome by the amendment of claims 1 and 3. The amended claim 1 now recites "said carrier macromolecule is water soluble at a temperature in the range of 0-60°C." The alleged water soluble carrier macromolecule in Dale is agarose. As recognized by the Examiner, agarose can only be dissolved in boiled water, not at a temperature in the range of 0-60°C. The amended claim 3 now recites "said carrier macromolecule is a natural gum or a homopolyamino acid." As recognized by the Examiner, Dale, at the most, discloses a primer bound to a cellulose. Dale does not disclose a primer bound to any other type of carrier macromolecule having a molecular weight in excess of 80,000 Daltons, let alone a natural gum or a homopolyamino acid as a carrier macromolecule.



It is respectfully submitted that the rejection of claims 1, 3-6, 18 and 21 under 35 U.S.C. § 102 is overcome by the above remarks and/or amendments and must be withdrawn.

### **Rejections under 35 U.S.C. § 103**

Claims 21 and 22 are rejected under 35 U.S.C. 103(a) as being allegedly unpatentable over McCormick *et al.*, (US Patent No. 4,760,017, published on July 26, 1988) in view of Yamane *et al.*, (US Patent No. 4,876,335, published on October 24, 1989).

McCormick is alleged to teach hybridizing a target nucleic acid to a single stranded nucleic acid immobilized on a support (see column 3). The Examiner acknowledges that McCormick does not disclose an immobilized nucleic acid as recited in claim 21 and using the immobilized nucleic acid as recited in claim 21 for hybridization.

Yamane is alleged to teach using a polylysine-labeled oligonucleotide for hybridization (see abstract). According to the Examiner, Lysine residues on the polylysine can be any desired numbers wherein the polylysine is covalently connected to the oligonucleotide (see column 2).

The Examiner alleges that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have made an immobilized nucleic acid comprising a nucleic acid linked via a covalent bond to a non-nucleotide carrier macromolecule having a molecular weight in excess of 80,000 Daltons (i.e., polylysine) as recited in claim 21 wherein the macromolecule is bound to a solid support and used the immobilized nucleic acid as recited in claim 21 as a hybridization probe in view McCormick and Yamane.

This rejection is respectfully traversed. McCormick and Yamane, whether alone or in combination, do not render the presently claimed invention obvious because there is no motivation, whether explicitly or implicitly, to combine the teachings of McCormick and Yamane to arrive at the presently claimed immobilized nucleic acids and methods using the same.



In fact, McCormick teaches away from such combination to arrive at the presently claimed invention. The test for “teaching away” is that a “reference will teach away if it suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant.” *In re Gurley*, 27 F.3d 551, 553, 31 USPQ.2D 1130, 1131 (Fed. Cir. 1994). In addition, if proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984) (Claimed device was a blood filter assembly for use during medical procedures wherein both the inlet and outlet for the blood were located at the bottom end of the filter assembly, and wherein a gas vent was present at the top of the filter assembly. The prior art reference taught a liquid strainer for removing dirt and water from gasoline and other light oils wherein the inlet and outlet were at the top of the device, and wherein a pet-cock (stopcock) was located at the bottom of the device for periodically removing the collected dirt and water. The reference further taught that the separation is assisted by gravity. The Board concluded the claims were *prima facie* obvious, reasoning that it would have been obvious to turn the reference device upside down. The Court reversed, finding that if the prior art device was turned upside down it would be inoperable for its intended purpose because the gasoline to be filtered would be trapped at the top, the water and heavier oils sought to be separated would flow out of the outlet instead of the purified gasoline, and the screen would become clogged.).

As recognized by the Examiner, McCormick teaches a method for identifying nucleic acid sequences comprises the steps of: (a) rendering the target nucleic acids single-stranded; (b) immobilizing the single-stranded nucleic acids onto a support; (c) allowing said single-stranded nucleic acids to hybridize with a single-stranded arabinonucleic acid probe; (d) washing said support to remove arabinonucleic acid not incorporated into the hybrid formed on the support; and (e) determining the presence of arabinonucleic acid in the hybrid formed on the support by contacting it with an antiarabinose antibody-label conjugate and detecting said label (*See* McCormick at column 3, lines 5-21; emphases added).

According to McCormick, the immobilized nucleic acid is the single-stranded target nucleic acid, which does not contain any non-nucleotide component. The only nucleic acid that contains a non-nucleotide component is the arabinonucleic acid probe. To ensure proper detection, *e.g.*, to prevent or reduce false positive signal, the free arabinonucleic acid probe must be removed from the support. If McCormick and Yamane were combined to arrive at the immobilized nucleic acids and methods of present claims 21 and 22, the arabinonucleic acid probe or the polylysine-labeled oligonucleotide must be bound on the support, as required by the present claims 21 and 22. This would, of course, totally defeat the purpose of the method taught in McCormick because the arabinonucleic acid probe is always bound to the support and cannot be used to detect a signal at all. Thus, contrary to the Examiner's assertion, the skilled artisans would not combine the teachings of McCormick and Yamane to arrive at the presently claimed immobilized nucleic acids and methods using the same.

In addition, to establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. MPEP 2143.03; and *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). Claim 21, in the presently amended form, requires that "the non-nucleotide carrier macromolecule is directly bound to a solid support." Neither McCormick nor Yamane teaches a non-nucleotide carrier macromolecule that is directly bound to a solid support. In McCormick, the arabinonucleic acid probe, at the most, is indirectly bound to the solid support via its hybridization with the target nucleic acid. In Yamane, the polylysine-labeled oligonucleotide is not bound to any support.

It is respectfully submitted that the rejection of claims 21 and 22 under 35 U.S.C. § 103 is overcome by the above remarks and/or amendments and must be withdrawn.

### **Claim 23**

New claim 23 incorporates the limitation of previously pending claim 7, which is free of prior art as indicated in the Final Office Action.

### CONCLUSION

Applicant submits that the objections to claims 1, 3, 7-10, 20 and 23, rejection of claims 7-17 under 35 U.S.C. § 112, the rejection of claims 1, 3-6, 18 and 21 under 35 U.S.C. § 102 and the rejection of claims 21 and 22 under 35 U.S.C. § 103 have been overcome by the above remarks and/or amendments. Early allowance of the pending claims 1 and 3-23 are earnestly requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 577212000101. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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